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(54) TEMPERATURE-SENSITIVE LIPOSOME PHARMACEUTICAL PREPARATION

(57)Abstract:

PURPOSE: To obtain a temperature-sensitive liposome pharmaceutical preparation capable of effectively releasing a medicine at 40-45°C.

CONSTITUTION: The temperature-sensitive liposome pharmaceutical preparation is obtained by sealing a medicine into a liposome having a molar ratio of a nonionic surfactant to a phospholipid of (1/100) to (30/100).

LEGAL STATUS

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CLAIMS

[Claim(s)]
[Claim 1] The mole ratio of a nonionic surface active agent and phospholipid Temperature sensitivity liposome pharmaceutical preparation which enclosed the drug with the liposome of 1 / 100 - 30/100.
[Claim 2] Temperature sensitivity liposome pharmaceutical preparation according to claim 1 whose nonionic surface active agent is an ether mold nonionic surface active agent.
[Claim 3] Temperature sensitivity liposome pharmaceutical preparation according to claim 1 whose nonionic surface active agent is an alkylphenol mold nonionic surface active agent.
[Claim 4] Temperature sensitivity liposome pharmaceutical preparation according to claim 1 whose nonionic surface active agent is a sorbitan ester ether mold nonionic surface active agent.

[Translation done.]

* NOTICES *

1.This document has been translated by computer. So the translation may not reflect the original precisely.
2.**** shows the word which can not be translated.
3.In the drawings, any words are not translated.

DETAILED DESCRIPTION

[Detailed Description of the Invention]
[0001]
[Industrial Application] This invention relates to the temperature sensitivity liposome pharmaceutical preparation which comes to enclose a drug. Since temperature sensitivity liposome has the description which emits an endocyst drug in the temperature requirement of the thermotherapy of a disease part when using as a chemotherapic drug of disease parts, such as cancer, it is useful as pharmaceutical preparation which can demonstrate the curative effect which the drug was distributed over the disease part with the small dose at high concentration, and heightened the drug delivery effectiveness in multiplication.
[0002]
[Description of the Prior Art] warming which was excellent with the advance of fields, such as a machine, electrical and electric equipment, and physical engineering, -- equipment is developed and only a target disease part in the living body can be warmed correctly -- as Since it is thought that an endocyst drug can be emitted from the liposome film in temperature dependence, and the drug of isolation can be distributed efficiently when it becomes, the temperature sensitivity liposome prescribed for the patient into the vein rides on a blood flow and it has been carried to the target disease part, development of temperature sensitivity liposome is made energetically. The purpose tumor site can be correctly warmed now and, as for the thermotherapy of cancer, the effectiveness is actually expected.
[0003] Since sufficient effectiveness of not only a warm temperature independent but a therapy is expected in this therapy, giving a chemotherapy to coincidence is also known (Jpn.J.Hyperthermic Oncol.2., No3, and 1986). The problem was in the stability and temperature responsibility as liposome, and the temperature sensitivity liposome reported conventionally was not enough as effectiveness. On the other hand, it is living body liquid osmotic pressure in the liposome whose membranous phase transition temperature is 40-45 degrees C in JP,2-1404,A. The drug content liquid of hypertonicity tends to be enclosed 1.2 - 2.5 times, and solution tends to be measured by making into the main constituent of the liposome film the phospholipid whose acyl group is a saturation acyl group. On the other hand, at JP,4-187634,A, it combined and used and solution is measured for the various phospholipid which has a saturated fatty acid acyl group as a membranous main constituent by independent or making phase transition temperature into 40-45 degrees C. moreover, the report which combined a thermotherapy and temperature sensitivity liposome -- [-- for example Cancer Treatment Reports, 71, 1053 (1987); Biochim.Biophys.Acta, 978, and 185-190(1989)], a report of emission of the endocyst object from the liposome by operation of a surfactant -- [-- for example Biochim.Biophys.Acta, 937 and 127-134 (1988); Colloids and Surfaces, 61 281-290 (1991); JAOSC68 No.5 315-319 (1991); J.Am.Chem.Soc.113, 7237-7240 (1991); Although there is J.of Coll.& Int.Sci.148 No.2 310-316(1992)] It is not known that temperature sensitivity will be size and the liposome which makes a constituent the phospholipid of this invention and both of a nonionic surface active agent will use this temperature sensitivity liposome as drugs of a thermotherapy.
[0004]

[Problem(s) to be Solved by the Invention] Although the liposome to which membranous phase transition temperature uses as base resin the phospholipid whose acyl group is a saturation acyl group at 40-45 degrees C uses the function in which will be in a liquid crystal condition by the gel state if it warms at 40-45 degrees C, although it is stable, and the drug by which embedding was carried out to the interior becomes is easy to be emitted by temperature, emission of a dramatic drug with a thermotherapy temperature of 40 degrees C or more is not seen. Therefore, the purpose of this invention is to offer the temperature sensitivity liposome pharmaceutical preparation which can emit a drug effectively at the temperature of 40-45 degrees C.

[0005]

[Means for Solving the Problem] a nonionic surface active agent invades between phospholipid molecules, and the appropriate liposome which was alike and combined phospholipid and a nonionic surface active agent causes the fall of the cooperativity of a phospholipid molecule. Although phase transition temperature is 38-42 degrees C and is stable by temperature, at 40-45 degrees C, the function in which the drug by which embedding was carried out is rapidly emitted to the interior can be used because it will be in a liquid crystal condition in addition to the fall of cooperativity.

[0006] If this invention is followed, the mole ratio of a nonionic surface active agent and phospholipid The temperature sensitivity liposome pharmaceutical preparation which enclosed the drug with the liposome of 1 / 100 - 30/100 is offered.

[0007] As an ether mold nonionic surface active agent, among the nonionic surface active agents used by this invention For example, the polyoxyethylene (4) lauryl ether, the polyoxyethylene (15) lauryl ether, The polyoxyethylene (20) lauryl ether, the polyoxyethylene (30) lauryl ether, The polyoxyethylene (8.5) tridecyl ether, the polyoxyethylene (7) milli still ether, The polyoxyethylene (8) cetyl ether, the polyoxyethylene (10) cetyl ether, The polyoxyethylene (13) cetyl ether, polyoxyethylene (6) stearyl ether, Polyoxyethylene (7) stearyl ether, polyoxyethylene (15) stearyl ether, Polyoxyethylene (220) stearyl ether, the polyoxyethylene (6) oleyl ether, the polyoxyethylene (15) oleyl ether, the polyoxyethylene (30) oleyl ether, etc. are raised.

[0008] As an alkylphenol mold nonionic surface active agent used by this invention For example, the polyoxyethylene (2) nonylphenyl ether, the polyoxyethylene (4.5) nonylphenyl ether, The polyoxyethylene (6) nonylphenyl ether, the polyoxyethylene (8.5) nonylphenyl ether, The polyoxyethylene (10) nonylphenyl ether, the polyoxyethylene (12) nonylphenyl ether, The polyoxyethylene (15) nonylphenyl ether, the polyoxyethylene (20) nonylphenyl ether, The polyoxyethylene (30) nonylphenyl ether, the polyoxyethylene (40) nonylphenyl ether, The polyoxyethylene (70) nonylphenyl ether, polyoxyethylene (4.5) octyl phenyl ether, Polyoxyethylene (6) octyl phenyl ether, polyoxyethylene (8) octyl phenyl ether, Polyoxyethylene (10) octyl phenyl ether, polyoxyethylene (15) octyl phenyl ether, polyoxyethylene (20) octyl phenyl ether, polyoxyethylene (40) octyl phenyl ether, etc. are raised.

[0009] As a sorbitan ester ether mold nonionic surface active agent used for this invention, polyoxyethylene (21) sorbitan monolaurate, polyoxyethylene (21) sorbitan monopalmitate, polyoxyethylene (21) sorbitan monostearate, polyoxyethylene (21) sorbitan monooleate, etc. are raised, for example. An ester mold nonionic surface active agent, a sorbitan ester mold nonionic surface active agent, a block polymer mold nonionic surface active agent, an alkylamine mold nonionic surface active agent, an alkylamide mold nonionic surface active agent, a polyglycerin mold nonionic surface active agent, etc. are raised to others. in addition, said various nonionic surface active agents carried out are independent -- it is -- carrying out -- it can combine and use.

[0010] if the phase transition temperature of the liposome formed considering phospholipid as a principal component as phospholipid which can be used by this invention, for example, without including a nonionic surface active agent is beyond thermotherapy temperature, any, such as phosphatidylcholine, sphingomyelin, phosphatidylethanolamine, phosphatidylserine, phosphatidylinositol, phosphatidylglycerol, soybean phosphatide, and yolk phospholipid, are sufficient, and these phospholipid is also independent -- it is -- carrying out -- it can be used by the combined combination.

[0011] A stearyl amine, a JISECHIRURIN acid, phosphatidic acid, a higher fatty acid, etc. can be further added to the liposome pharmaceutical preparation of this invention as sterols and electric charge matter, such as cholesterol and a cholestanol, as a film stabilizing agent. Moreover, need components, such as an anti-oxidant, can be added for preservation stability.
[0012] this invention -- setting -- mole ratio of a nonionic surface active agent and phospholipid 1 / 100 - 30/100 -- desirable -- It is 5 / 100 - 20/100. This mole ratio If smaller than 1/100, the engine performance of the purpose will not be demonstrated, and if larger than 30/100, formation of a lipid duplex film will become difficult, and the temperature sensitivity liposome pharmaceutical preparation made into the purpose is not obtained.
[0013] As a drug used in this invention, an antitumor agent is a desirable object drug. As an example of such a drug, cisplatin, carboplatin, Metal complexes, such as tetra-PURACHIN and IPUROPURACHIN, adriamycin, A mitomycin, an actinomycin, ansamycin, PUREO mycin, Antitumor antibiotics, such as Ara-C and a daunomycin, 5-FU, methotrexate, Alkylating agents, such as antimetabolites, such as TAC-788, BCNU, and CCNU, The lymphokine like the anticancer agent of others, such as melphalan and mitoxantrone, a natural mold, interferon (alpha, beta, gamma) and a natural mold, or gene recombination mold interleukin 2 is raised.
[0014] The mole ratio of a nonionic surface active agent and phospholipid It is not special to the manufacture approach of the liposome which is 1 / 100 - 30/100 itself, and it can be manufactured using well-known techniques, such as an ultrasonic irradiation method and the extruder method.
[0015] Below, the preparation approach of the liposome by the ultrasonic irradiation method is shown as an example. That is, first, a phosphate buffer can be added to phospholipid and a nonionic surface active agent, ultrasonic irradiation can be carried out, cooling using bus mold supersonic-wave irradiation equipment, and a liposome solution can be obtained by next using and filtering a filter at a room temperature. On the other hand, in preparing the liposome by the extruder method, after dissolving phospholipid and a nonionic surface active agent into chloroform, a solvent is removed using a rotary evaporator and it carries out reduced pressure drying one whole day and night. Next, a desired liposome solution can be obtained by adding a phosphate buffer, stirring violently using a vortex mixer, and extruding the obtained multilamellar liposome dispersion liquid by the extruder equipped with a polycarbonate film.
[0016]
[Example] It cannot be overemphasized that it is not what limits the range of this invention to these examples hereafter although an example explains this invention further.
[0017] an example -- one (temperature sensitivity liposome) -- dipalmitoylphosphatidylcholine (DPPC) -- a polyoxyethylene -- (-- ten --) -- cetyl -- the ether -- [-- C -- 16 -- (-- EO --) -- ten --] -- mixing -- a lipid -- Table 1 -- having been shown -- a rate -- blending -- the carboxy (fluorescein CF) content pH 7.4 Output 80w was ultrasonicated for 30 minutes 50 degrees C in 20ml of 0.01M phosphate buffers. It is sepharose about this thing. Gel filtration was performed using CL-2B and temperature sensitivity liposome pharmaceutical preparation was obtained. This temperature sensitivity liposome pharmaceutical preparation It diluted with the 0.01M phosphate buffer 20 times, temperature was kept at 42-43 degrees C, aging of the fluorescence intensity of CF leaked from liposome pharmaceutical preparation was measured, and it considered as the amount of liposome film transparency. In addition, measurement of the phase transition temperature (Tc) of temperature sensitivity liposome pharmaceutical preparation performed liposome sample 70microl using the scan mold differential calorimeter (Seiko SSC5200 DSC120) for the sampler (programming-rate 1degree C/min.). A result is shown in Table 1.
[0018] Example of comparison 1C16 (EO) 10 is placed and changed into phosphatidic acid (PA), and it is PA/DPPC=10/100. It blended at a rate and also liposome was obtained like the example 1. A result is shown in Table 1.
[0019]
[Table 1]

	組　成（モル比）	Tc（℃）	カルボキシフルオレッセイン透過量（%）		
			5分後	15分後	30分後
実施例1	$C_{16}(EO)_{10}$／DPPC 20/100	38.6	100	-	-
	15/100	39.3	100	-	-
	10/100	40.0	94	-	-
	6/100	40.5	42	68	86
比較例	PA／DPPC 10/100	41.7	4	8	9

[0020] Example 2C16 (EO) The polyoxyethylene (7) milli still ether [C14(EO)7] was used instead of 10, and also temperature sensitivity liposome pharmaceutical preparation was obtained by the same approach as an example 1, and the amount of liposome film transparency was measured. A result is shown in Table 2.

[0021]

[Table 2]

	組　成（モル比）	Tc（℃）	カルボキシフルオレッセイン透過量（%）		
			5分後	15分後	30分後
実施例2	$C_{14}(EO)_{7}$／DPPC 20/100	38.9	100	-	-
	15/100	39.5	100	-	-
	10/100	40.2	95	-	-
	6/100	41.1	43	69	85

[0022] Used DPPC/JISUTE aroyl phosphatidylcholine (DSPC) =95 / 5 (Wt%) instead of example 3DPPC, and polyoxyethylene (10) octyl phenyl ether [C9 Phe (EO)10] was used instead of C16(EO)10, and also temperature sensitivity liposome pharmaceutical preparation was obtained by the same approach as an example 1, and the amount of liposome film transparency was measured. A result is shown in Table 3.

[0023]

[Table 3]

	組　　成 （モル比）	Tc (℃)	カルボキシフルオレッセイン透過量 (%)		
実	$C_9Phe(EO)_{10}$/[(DPPC/DSPC=95/5(Wt%))]		5分後	15分後	30分後
施	20/100	38.4	100	-	-
例	15/100	39.0	100	-	-
	10/100	40.2	92	-	-
3	6/100	40.7	45	71	88

[0024] Used high grade yolk lecithin (EPC) / DSPC=20 / 80 (Wt%) instead of example 4DPPC, and polyoxyethylene (21) sorbitan monolaurate [C12Sor (EO)21] was used instead of C16(EO)10, and also temperature sensitivity liposome pharmaceutical preparation was obtained by the same approach as an example 1, and the amount of liposome film transparency was measured. A result is shown in Table 4.

[0025]

[Table 4]

	組　　成 （モル比）	Tc (℃)	カルボキシフルオレッセイン透過量 (%)		
実	$C_{12}Sor(EO)_{21}$/[(EPC/DSPC=20/80(Wt%))]		5分後	15分後	30分後
施	20/100	38.4	100	-	-
例	15/100	39.0	100	-	-
	10/100	40.2	95	-	-
4	6/100	40.7	47	73	91

[0026]
[Effect of the Invention] Since it will be in a liquid crystal condition in addition to the fall of the cooperativity of the phospholipid which constitutes liposome from 40-45 degrees C, the liposome of this invention serves as temperature sensitivity liposome pharmaceutical preparation with the function in which drugs, such as an anticancer agent by which embedding was carried out, are rapidly emitted to the interior.

[Translation done.]